Featured Article

Results of a Multicenter Randomized Phase II Trial of Thalidomide and Prednisone Maintenance Therapy for Multiple Myeloma after Autologous Stem Cell Transplant

A. Keith Stewart,1 Christine I. Chen,1 Kang Howson-Jan,2 Darrell White,3 Jean Roy,4 Michael J. Kovacs,2 Chaim Shustik,5 Anna Sadura,6 Lois Shepherd,6 Keyue Ding,6 Ralph M. Meyer,7 and Andrew R. Belch8

1Princess Margaret Hospital, Toronto, Ontario, Canada; 2London Health Sciences Centre, London, United Kingdom; 3Nova Scotia Cancer Centre, Halifax, Nova Scotia, Canada; 4Maisonneuve-Rosemont Hospital, Montreal, Quebec, Canada; 5McGill Oncology Group, Montreal, Quebec, Canada; 6National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada; 7Hamilton Regional Cancer Centre, Hamilton, Ontario, Canada; and 8Cross Cancer Institute, Edmonton, Alberta, Canada

ABSTRACT

We report a multicenter, randomized phase II trial conducted to assess the tolerability of combined thalidomide and prednisone maintenance in multiple myeloma. Eligibility required administration of melphalan (200 mg/m²) with blood stem cell support within 1 year of treatment onset and initiation of maintenance within 60 to 100 days after stem cell infusion. All patients received 50 mg of prednisone by mouth on alternate days and thalidomide at a starting dose of either 200 or 400 mg daily by mouth. The primary end point was the incidence of dropout or dose reduction due to treatment toxicity within 6 months. Sixty-seven patients were enrolled. Median follow-up is 36.8 months. The primary end point was reached by 31% of patients on the 200 mg of thalidomide arm and 64% of patients on the 400 mg of thalidomide arm. Allowing for dose reduction, 76% of patients assigned to the 200 mg of thalidomide arm and 41% of patients assigned to the 400 mg of thalidomide arm remained on any maintenance therapy 18 months after registration. Eighty-eight percent of all patients dose-reduced thalidomide and 72% of all patients dose-reduced prednisone within 2 years of beginning maintenance. The median progression-free survival post-transplant is 32.3 months, or 42.2 months from diagnosis. Only the 200 mg of thalidomide arm of this trial met our definition of a tolerable maintenance therapy, defined as no dose reductions or discontinuation due to toxicity in at least 65% of patients for a minimum of 6 months, thus establishing a dosing schedule for phase III trials.

INTRODUCTION

Patients with multiple myeloma (MM) benefit from the early administration of high-dose chemotherapy supported by autologous stem cell transplantation (ASCT; refs. 1–5). Two large randomized trials have compared ASCT with standard doses of chemotherapy. Overall 5-year survival was improved from 12% to 52% in one trial, and median survival was improved from 42 to 54 months in the second trial. Despite these benefits, a continuous pattern of relapse post-transplantation is observed; for example, in the randomized trial with the longest reported follow-up, 61% of patients have relapsed within 5 years (2). Thus, an important and as yet unanswered question is to determine whether therapy that includes transplantation can be modified to further consolidate responses and improve survival. The potential benefits of maintenance therapy are particularly intriguing because the transplantation process may lead to very low tumor burdens that might be sensitive to longer-term therapy. In addition, emerging modalities of myeloma therapy may be well suited for use as maintenance therapy because these drugs are delivered orally and possess unique mechanisms of action.

Interferon-α has been tested as maintenance therapy after standard-dose chemotherapy in a meta-analysis of randomized trials, antitumor activity was demonstrated, but the magnitude of this benefit was small, and the drug is known to be associated with substantial treatment-related toxicity (6). Interferon-α was also used as maintenance therapy in both of the randomized trials demonstrating benefit of autologous transplantation (2, 3); however, data from one large randomized trial of interferon-α after ASCT demonstrates no survival benefit (7). Thus, given the toxicity of this drug and the negative results of randomized trials testing for potential benefit, maintenance therapy with interferon-α after transplantation is not considered to be a standard practice.

Corticosteroids are a class of drugs that could have potential benefits as maintenance therapy post-transplantation. In a randomized trial comparing 50 mg of prednisone with 10 mg of prednisone given on alternate days as maintenance therapy for patients who had received conventional-dose chemotherapy, both progression-free and overall survivals were superior in patients receiving 50 mg of prednisone on alternate days (8). A second randomized trial, reported in preliminary abstract form, has also described prolongation of progression-free survival in...
patients receiving a corticosteroid as maintenance therapy after conventional-dose treatment (9). No studies testing maintenance therapy with corticosteroids post-transplantation have been reported.

Thalidomide is another agent that could have benefits as maintenance therapy post-transplantation. In initial reports of testing thalidomide in patients with myeloma, including those with progressive disease post-transplantation, responses were observed in 37% of patients, with 14% achieving a complete or near complete remission (10). The doses used in these patients involved increases from 200 mg to 800 mg per day every 2 weeks if tolerated. The virtual absence of myelosuppressive toxicity suggests that thalidomide could be used in combination with cytotoxic agents and/or corticosteroids and that administration as maintenance therapy might be possible. Nevertheless, use of thalidomide is also associated with dose-dependent toxicities, and an appropriate dose of this drug to be used in a potential maintenance setting post-transplantation is unknown (11, 12). Indeed, there is a general paucity of carefully conducted prospective dose-finding and toxicity studies with this agent, leading to much uncertainty about an appropriate starting and maintenance dosing regimen.

Based on this background, the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) elected to test the combination of thalidomide given daily and prednisone (50 mg) given on alternate days as maintenance therapy in patients with MM who had received initial treatment that included high-dose melphalan with ASCT. Because there are uncertainties about the long-term tolerability of the prednisone and thalidomide combination, and given the specific uncertainties of the appropriate therapeutically active dose of thalidomide in this situation, we first elected to complete a dose-finding study before considering a larger phase III randomized trial. Given the unique circumstances of testing this combination of agents as maintenance therapy, we chose to use a randomized phase II design to select a preferred dose of thalidomide to eventually test in the phase III setting. We now report the results of this multicenter randomized phase II trial that evaluates two thalidomide doses, 200 and 400 mg, in combination with prednisone (50 mg) on alternate days, as maintenance therapy in patients with MM who have undergone ASCT. To our knowledge this is the first reported trial to formally address the use of prednisone and thalidomide in the post-transplant maintenance setting.

PATIENTS AND METHODS

The objective of this trial was to determine whether 200 mg of thalidomide and/or 400 mg of thalidomide, in combination with 50 mg of prednisone on alternate days, could be adequately tolerated as long-term maintenance therapy for patients with MM who had undergone ASCT. The primary outcome was to assess the proportion of patients discontinuing therapy or reducing the dose of therapy due to treatment-related toxicity observed within 6 months of commencing maintenance treatment. Secondary objectives included time to dose reduction or discontinuation for either or both study medications, a specific assessment of toxicities, and the combined progression-free and overall survivals for all patients.

**Trial Design and Study Population.** The MY-9 trial of the NCIC-CTG was a multicenter, nonblinded, randomized phase II dose-finding trial. The institutional review boards of all participating centers approved the study, and all patients provided written informed consent before registration. Eligibility required a previously documented diagnosis of MM as determined by biopsy of an osteolytic lesion or soft tissue tumor composed of plasma cells or the presence of at least 10% plasma cells observed within a bone marrow aspirate or biopsy. In addition, a quantifiable serum monoclonal paraprotein of any amount or 24-hour urinary excretion of at least 1 g of light chain was required. Patients with <10% plasma cells within the bone marrow could be eligible if there was at least one lytic lesion observed on skeletal survey radiographs and the above-mentioned criteria for a serum or urine M-protein were satisfied. Patients were required to have received high-dose melphalan at 200 mg/m² followed by ASCT as part of their initial treatment program, with transplantation performed within 1 year of beginning treatment. No prior thalidomide was allowed. Registration on to this study was required within 60 to 100 days of the stem cell reinfusion date. Eligibility criteria at the time of registration included an Eastern Cooperative Oncology Group performance status (13) of <3, granulocytes of at least 1.0 × 10⁹ per liter, serum liver enzymes and bilirubin values of <2 × the upper limit of normal, and serum creatinine value of <3 × the upper limit of normal, and women of child-bearing age were required to have a negative pregnancy test and to have signed consent agreeing to comply with medically approved birth control. Exclusion criteria included a prior or concurrent malignancy, diabetes with end organ damage, uncontrolled hypertension, a history of gastric ulceration or bleeding, avascular necrosis of the hips, neuropathy causing symptomatic dysfunction, prior use of thalidomide, or ongoing employment that prohibited the use of sedatives. Baseline evaluations at registration included a history and physical examination, routine chemistry and hematology, serum and urine immunoelectrophoresis or immunofixation and paraprotein quantitation, skeletal survey radiographs, and a bone marrow aspirate. Patients were stratified by age greater than or less than 60 years and centrally randomized using a concealed process through use of computer-generated random numbers.

**Treatment Protocol.** Patients were randomized to receive either 200 or 400 mg of thalidomide daily, taken orally at night; all patients received 50 mg of prednisone taken orally on alternate days. In keeping with practice norms at the time of the study design, patients assigned to receive 200 mg of thalidomide began therapy with this dose; those assigned to receive 400 mg of thalidomide began therapy with 200 mg of thalidomide per day for 2 weeks and then had the dose escalated to 400 mg of thalidomide. Dose reductions of thalidomide in 50- to 100-mg increments to a minimum dose of 100 mg were allowed for treatment-related toxicity. A one-time dose reduction of prednisone to 25 mg on alternate days was also permitted. A specific dose attenuation schedule for each agent was used; toxicity was graded using National Cancer Institute Common Toxicity Criteria. Concurrent bisphosphonates, H₂ blockers, and laxatives were recommended. Anticoagulants were not routinely used. Patients were monitored monthly for 6 months, then monitored every 3 months for 2 years, and then monitored every 6 months.
until progression or death. Myeloma restaging was performed every 6 months or at the time of suspected clinical progression.

Assessment of Outcomes. The primary outcome measure was the proportion of patients in each of the randomized groups who either discontinued or dose-reduced thalidomide or prednisone due to National Cancer Institute Common Toxicity Criteria grade 2 or greater treatment-related toxicity that occurred within 6 months of beginning maintenance treatment. In each case of a dose reduction or discontinuation of study therapy, the responsible physician was asked whether the toxic reaction was primarily attributable to thalidomide, prednisone, or both drugs. A secondary outcome measure was the time to dose reduction or discontinuation of either drug. This was measured from the time of randomization until the time of the first dose modification that was due to treatment-related toxicity. This outcome measure was subanalyzed by thalidomide or prednisone, based on the determination made by the responsible physician.

Additional secondary outcomes included the pooled progression-free and overall survivals of the two randomized groups. Progression-free survival was measured as the time from randomization until documented first disease progression. Criteria for disease progression included an increase of the serum paraprotein by 50% or an absolute increase of 10 g or more per liter from the nadir (maximum) response; an increase of the 24-hour urine paraprotein by 100% or an absolute increase of 2 g or more per 24 hours from the nadir response, new onset of hypercalcemia considered to be due to myeloma, or an unequivocal new lytic bone lesion. A new vertebral body compression fracture was not a sufficient criterion for disease progression. Overall survival was measured as the time from randomization until death due to any cause. The trial was not designed to compare the progression-free or overall survivals of the two randomized groups.

Response criteria were graded as per Blade et al. (14), with the notable exception that bone marrow aspirates (although requested as part of the study) were not available on all patients at the 6 and 12 month evaluation points. In patients without a bone marrow aspirate at those time points, serum and urine paraprotein levels and immunofixation were used to grade response.

Statistical Analyses. All eligible patients were included and analyzed on an intention to treat basis. A randomized phase II trial design was used to assess the feasibility of the specific treatment regimens in each of two patient cohorts. This design was used to minimize bias of patient entry to each of the cohorts; the trial was not designed to permit a comparison of the two randomized groups, nor was there sufficient statistical power to do so. A two-stage design was used to determine patient accrual (15). It was assumed that this regimen would not be of further interest and that additional phase III testing would be concluded that use of this regimen as maintenance therapy was not feasible. If ≤6 patients experienced a dose reduction or treatment discontinuation, 20 additional patients (total, 40) would be entered on to this arm. The trial was designed to have 90% power to reject a rate of dose reduction or treatment discontinuation that was >33% and to have a 95% chance of accepting a rate of dose reduction or treatment discontinuation that was <14%.

Time to events, including dose reduction or treatment discontinuation and progression-free and overall survivals, was calculated using the actuarial method of Kaplan and Meier (16).

Data Preparation and Analysis. Enrollment was from July 2000 to September 2001. At study closure, all patients had been followed for >6 months, unless they died or discontinued therapy within 6 months of their registration date. Analyses of pretreatment characteristics, dose reduction, or treatment discontinuation and efficacy analyses such as progression-free and overall survivals were based on all eligible patients. Safety and drug exposure analyses were performed on all patients who received at least one dose of study therapies. All analyses were by treatment arm, except for progression-free and overall survivals; these outcomes were evaluated by combining the two treatment arms.

RESULTS

Recruitment and Baseline Characteristics. Sixty-seven patients were accrued from 13 centers; 22 were randomized to receive 400 mg of thalidomide daily, and 45 were randomized to receive 200 mg of thalidomide daily. Because of an excess of treatment-related toxicity, entry to the 400-mg dose arm was closed after completing the first stage of the projected sample size. Side effects resulting in discontinuation or dose reduction were commonly fatigue and drowsiness. All patients are included in this analysis; their pretreatment characteristics are summarized in Table 1 and are balanced between the randomized groups. The median follow-up was 36.8 months.

Treatment Received. In the group allocated to receive 400 mg of thalidomide, the number of patients experiencing a dose reduction or treatment discontinuation due to treatment-related toxicity within 6 months of commencing therapy was 14

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics at study entry by arm of the trial</th>
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<tr>
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</tr>
<tr>
<td>II</td>
<td>14 (31)</td>
</tr>
<tr>
<td>III</td>
<td>27 (60)</td>
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</table>

NOTE. Values represent n (%).
of 22 patients [64%; 95% confidence interval (CI), 45–83%]. Fifteen patients on this arm dose-reduced or discontinued drug within 6 months for any reason (i.e., including noncompliance or disease progression), 13 of whom (59% of all patients and 87% of those requiring a dose modification) required a dose reduction or discontinuation of thalidomide, and 11 of whom (50% of all patients and 73% of those requiring a dose modification) required dose modifications of prednisone (Table 2). In the group allocated to receive 200 mg of thalidomide, 14 of 45 patients (31%; 95% CI, 20–47%) required a dose reduction or discontinued treatment due to treatment-related toxicity within 6 months of commencing therapy. Overall, 24 patients on this arm dose-reduced or stopped drug for any reason, 18 of whom required modifications or discontinued thalidomide (40% of all patients and 75% of those requiring a dose modification), and 21 of whom required dose modifications of prednisone (46% of all patients and 88% of those requiring a dose modification; Table 2).

We also conducted secondary exploratory analyses to assess the time to dose reduction or discontinuation of therapy (Figs. 1 and 2). The median time to dose reduction or discontinuation of either of the study drugs was 2.1 months for patients allocated to receive 400 mg of thalidomide and 5.5 months for those allocated to receive 200 mg of thalidomide. The median times to modifying prednisone therapy were similar between the two treatment groups: 6.9 months for those allocated to receive 200 mg of thalidomide and 8.3 months for those allocated to receive 200 mg of thalidomide (Fig. 1). In contrast, the median time to modifying the dose of thalidomide appeared to be shorter in those allocated to receive 400 mg of thalidomide (4.0 months) in comparison with those allocated to receive 200 mg of thalidomide (9.7 months; Fig. 2).

Finally, we also evaluated the two treatment groups with respect to the duration of treatment with any dose of thalidomide (Table 2). After 6 months of follow-up, 15 patients (68%) randomized to receive 400 mg of thalidomide remained on the planned or an attenuated dose; in the 200-mg arm, 36 patients (80%) continued on any dose of the drug. By 18 months, 9 patients in the 400-mg arm (41%) and 34 patients in the 200-mg arm (76%) continued to take any dose of thalidomide. Only eight patients in the 200-mg arm (18%) continued on their initial starting dose for the duration of the study. The median cumulative dose of thalidomide received is 83.5 g (range, 16–1,626 g) on the 200-mg arm, whereas it is 76.9 g (range, 66–3,520 g) on the 400-mg arm. This translates into a median daily dose of 133 versus 320 mg per arm. Thus, patients on the higher thalidomide starting dose cumulatively received less drug overall as a consequence of toxicity. The significance of dose versus longevity of treatment is unknown in this setting.

Response, Progression-Free Survival, and Overall Survival. This study was not designed to compare the two randomized groups with respect to response to treatment, progression-free survival, or overall survival. However, we did evaluate these outcomes by pooling the two treatment groups for the purposes of obtaining estimates of whether any dose of thalidomide plus prednisone might provide a benefit in comparison with reported results. Using the previously published Blade et al. criteria (14) for evaluation of response, 15% of patients at study entry had attained a complete or near complete remission post-transplantation. During follow-up, the best response achieved was upgraded in 53% of evaluable patients, with 38% assessed as achieving a complete or near complete remission 1 year after study entry. Note that bone marrow evaluation was not available on all patients at the 1 year time point, and response is graded on the basis of serum and urine paraprotein and immunofixation measurement only. Because there is no comparator arm, the contribution of maintenance therapy versus the recognized phenomenon of delayed response after transplant cannot be determined.

The median time from diagnosis to study entry was 9.9 months. Measured from the time of study entry, the 1-year progression-free and overall survivals for all enrolled patients were 81% (95% CI, 71–90%) and 91% (95% CI, 84–98%) respectively (Fig. 3). Thirty-six of the 67 patients have progressed. The median progression-free survival from transplant is

| Table 2 Drug dose modifications or discontinuation by arm of trial |
|-----------------------------|-----------------------------|-----------------------------|
| Outcome                      | 200 mg of thalidomide (n = 45) | 400 mg of thalidomide (n = 22) |
| Dose modification or discontinuation due to toxicity at 6 months | 31% | 64% |
| Dose modification for any reason at 6 months | | |
| Dose modification, thalidomide only | 53% | 68% |
| Dose modification, prednisone only | 40% | 59% |
| Time to any dose modification | | |
| Median (mo) | 5.5 | 2.1 |
| No dose modification at 6 months | 47% | 32% |
| Time to thalidomide dose modification | | |
| Median (mo) | 9.7 | 4.0 |
| No thalidomide dose modification at 6 months | 60% | 41% |
| Any drug discontinuation at 2 years (total) | 60% | 86% |
| Drug discontinuation, thalidomide only | 47% | 82% |
| Drug discontinuation, prednisone only | 53% | 68% |
| Time to any drug discontinuation | | |
| Median (mo) | 14.5 | 7.3 |
| No drug discontinuation at 6 months | 78% | 61% |
| Time to thalidomide dose discontinuation | | |
| Median (mo) | 80% | 68% |
| No thalidomide discontinuation at 6 months | Not reached | 7.9 |
32.3 months (42.2 months from diagnosis). Seventeen of the 67 patients have died with median overall survival not reached.

**Toxicities and Causes of Death.** Participants who received at least one dose of study medication were included in the safety analysis. During the first 6 months of therapy, grade 1 and 2 toxicities were frequently observed and included neuropathy (54%), constipation (42%), fatigue (37%), dizziness (34%), infection (30%), sedation (22%), xerostomia (22%), skin rash (20%), and edema (19%). Reported reasons for drug discontinuation are outlined in Table 3. Severe nonhematologic toxicities (grade 3 or 4) are summarized in Table 4 and were observed in 36% of patients allocated to receive 400 mg of thalidomide and 27% of those allocated to receive 200 mg of thalidomide. Symptomatic venous thrombotic events were observed in five patients (7.5%). Fifteen deaths have been observed, with 12 attributed to progressive myeloma, 1 to disseminated varicella with hepatitis, and 2 to secondary malignancies (non-Hodgkin’s lymphoma and small-cell lung cancer).

**DISCUSSION**

Practice patterns for using maintenance treatments after high-dose chemotherapy and ASCT for patients with MM are highly variable. This is not surprising because there is insufficient evidence from randomized controlled trials to either support or dismiss a role for maintenance therapy within this context. In two large randomized trials comparing a transplantation strategy with conventional-dose chemotherapy, interferon-α was used in all patients after transplantation (2, 3). The role of maintenance therapy with interferon-α after transplantation has been evaluated in one large and appropriately powered...
randomized trial, in which no benefit to maintenance was observed (7).

Corticosteroids are highly active agents in treating patients with myeloma and may have a potential role as maintenance therapy. Indeed, steroid maintenance has been examined in two randomized studies after conventional chemotherapy. Berenson et al. (8) have reported prolongation of progression-free survival (14 versus 5 months; P = 0.003) and overall survival (37 versus 26 months; P = 0.05) in patients randomized to higher dose prednisone. In addition, a NCIC-CTG study of steroid maintenance after conventional therapy has observed significant prolongation of progression-free survival, but not overall survival, in patients randomized to receive maintenance dexamethasone (2.8 versus 2.0 years; P = 0.0001; ref. 9). On the basis of the results reported by Berenson et al. (8), we included 50 mg of prednisone given on alternate days in this study testing maintenance therapy by combining thalidomide with a corticosteroid.

Corticosteroids and thalidomide are being used in combination with increasing frequency in treating patients with myeloma (16–18). For example, Rajkumar et al. (17) have reported the results of treating 50 newly diagnosed patients with thalidomide at initial doses of 200 mg daily for 2 weeks with subsequent dose increases in 200 mg increments at 2-week intervals to a maximum daily dose of 800 mg. The response rate observed on this induction therapy was 64%. Grade 3 or 4 toxicities were seen in 32% of patients, with 12% of patients developing deep venous thrombosis. In a second study, Weber et al. (19) reported the outcomes of 68 previously untreated patients treated with thalidomide as a single agent (28 patients) or in combination with dexamethasone (40 patients). Responses were observed in 36% of patients treated with the single agent and 72% of those receiving the combination; responses occurred more rapidly in those receiving combination therapy. In these 68 patients, 17 grade 3 or 4 toxicities were observed, including thromboembolic events in 7 patients (10%).

Thalidomide is thus a very active agent in treating patients with myeloma, and a potential candidate for use in maintenance situations, particularly when combined with corticosteroids; however, significant toxicities are common. Furthermore, there are no reports of results of prospective, systematic testing of thalidomide as a maintenance therapy in patients who have undergone ASCT. Indeed the use of thalidomide in conjunction with corticosteroids as a maintenance therapy after ASCT may pose significant issues of tolerance and compliance in comparison with using the drug to treat active disease. We therefore concluded that prospective testing for feasibility was required if this combination of agents was to be considered for testing in the phase III setting.

We report here the results of using daily thalidomide in combination with alternate day prednisone as maintenance therapy post-ASCT. Using a randomized phase II design to minimize bias in assigning the dose of therapy, we have evaluated the feasibility of administering two different daily doses of thalidomide, 200 or 400 mg. Our data demonstrate that a daily thalidomide dose of 400 mg given in combination with 50 mg of prednisone on alternate days is not sustainable because 68% of patients required a dose modification within 6 months of commencing therapy, and the median time to requiring a dose adjustment of thalidomide was 4 months. Use of thalidomide at a dose of 400 mg per day also appeared to jeopardize the long-term use of the drug because only 41% of patients remained on any dose of thalidomide at 18 months. This limitation was observed despite using a starting dose of 200 mg per day for the first 2 weeks of therapy, with subsequent escalation of the therapy to 400 mg per day. In addition to being intolerable for most patients, grade 3 or 4 toxicities were observed in 36% of patients. In contrast, use of thalidomide at a dose of 200 mg per day was associated with a greater potential for use as maintenance therapy. Whereas 31% of patients did require a dose

<table>
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<tr>
<th>Table 3</th>
<th>Reasons for discontinuation of either or both protocol drugs by MY-9 patients because of toxicity</th>
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</thead>
<tbody>
<tr>
<td>Reason cited</td>
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<td>Dizziness</td>
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<td>Anxiety/agitation/mood changes</td>
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<td>Hyperglycemia/diabetes II</td>
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<tr>
<td>Muscle weakness</td>
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</tr>
<tr>
<td>Rash</td>
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</tr>
<tr>
<td>Recurrent infections</td>
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<tr>
<td>Bone or joint pain</td>
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</tr>
<tr>
<td>Total reasons cited</td>
<td>11</td>
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</table>

* One of the patients who discontinued thalidomide due to toxicity did so several months after completion of 2 years on both drugs.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Grade 3 and 4 toxicities by study arm</th>
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<tbody>
<tr>
<td>200 mg of thalidomide</td>
<td>400 mg of thalidomide</td>
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<tr>
<td>Grade 3 (n = 45)</td>
<td>Grade 4 (n = 43)</td>
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<tr>
<td>Flu-like symptoms</td>
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<td>Dermatology</td>
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<td>All events</td>
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modification of thalidomide or prednisone within 6 months of commencing therapy, 76% of patients remained on some dose of thalidomide 18 months after commencing therapy.

Secondary objectives of our trial were to assess efficacy outcomes and to evaluate toxicity. Our data demonstrate that in patients using thalidomide in combination with alternate day prednisone as a maintenance therapy, an upgrade in best response obtained was observed in 53% of patients evaluated 1 year after commencing maintenance therapy, with 38% assessed as achieving a complete or near complete remission 1 year after study entry. Because there is no comparator arm, the contribution of maintenance therapy versus the recognized phenomenon of delayed response post-transplant cannot be determined; however, review of the literature reveals that complete response rates of 44% to 48% one year after melphalan 200 mg/m² with interferon maintenance are expected, and thus our experience is similar to the reported literature (1–5). Because evaluation of response is often difficult in myeloma, only carefully conducted randomized trials using appropriate doses of drugs that retain meaningful activities with acceptable toxicities will determine the value of maintenance therapies.

Side effects were predictable and similar to those reported previously by others (16–23), e.g., our data suggest that use of thalidomide can be associated with the occurrence of important nonhematologic toxicities, including a risk of thromboembolic complications; in our study, this toxicity was observed in 7.5% of patients.

In summary, this prospective randomized phase II trial demonstrates that use of thalidomide doses of 200 mg per day in combination with 50 mg of prednisone given on alternate days is tolerable as a maintenance therapy after ASCT using our predefined criteria of having no dose modification or discontinuation within the first 6 months of therapy in 65% of patients. Indeed, with dose reductions permitted, 76% of patients assigned to receive 200 mg of thalidomide daily and 50 mg of prednisone on alternate days remained on maintenance therapy that included some dose of thalidomide 18 months after commencing therapy. Based on our results, we have activated a randomized phase III trial comparing 200 mg of thalidomide per day in combination with 50 mg of prednisone given on alternate days in comparison with observation in patients with myeloma who undergo ASCT as part of their initial therapy. We conclude that there are sufficient data to support the hypothesis that maintenance strategies that use thalidomide and corticosteroids after ASCT will improve outcome for myeloma patients. Nevertheless, until randomized trials provide unequivocal evidence of benefit, particularly given the potential for significant toxic reactions, treatment with thalidomide as maintenance therapy in the post-transplantation setting is not currently recommended unless it is part of a clinical trial.

REFERENCES
Results of a Multicenter Randomized Phase II Trial of Thalidomide and Prednisone Maintenance Therapy for Multiple Myeloma after Autologous Stem Cell Transplant


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